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I, JANENE PEISKER, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2004901161 for a patent by MICHAEL FRANCIS O'ROURKE as filed on 05 March 2004.

WITNESS my hand this
Seventh day of April 2005

JANENE PEISKER
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P00009
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Patents Act 1990

PROVISIONAL SPECIFICATION FOR THE INVENTION ENTITLED:

METHOD AND APPARATUS FOR DETERMINATION OF CARDIAC OUTPUT FROM THE ARTERIAL PRESSURE PULSE WAVEFORM

This invention is described in the following statement:-

This invention relates to the determination of cardiac (flow) output from the heart through analysis of the pressure or diameter waveform in the upper limb (radial, brachial or subclavian artery) or in the neck (carotid artery).

A clinical and scientific goal for many years has been to measure the cardiac output (blood flow ejected) by the heart per minute. The arterial pressure and diameter pulse waveform is created by this ejection, but on account of differences in arterial properties with age, differences in the pattern of flow ejection of the heart with age and with weakening of left ventricular muscle, this goal has not been attained with precision.

Additional problems include the effects of wave travel and reflection in the arterial tree which cause variable amplification of the pressure pulse between central and peripheral arteries. This has been addressed by Kelly and Fitchett, J Am Coll Cardiol 1992;20:952-63, van Bortel et al., J Hypertens 2001;19:1037-44, Pauca, Kon and O'Rourke, Br J Anaesth 2004 (in press), and by other methods eg. US patent No. 5,265,011.

The object of the present invention is to overcome all major problems created by aging and cardiac disease, as well as pressure pulse amplification in the more peripheral arteries, so that the radial or brachial arterial pulse, transformed to the aortic pulse, or the carotid or subclavian pulse in the neck, can be used to calculate the velocity of blood ejection from the heart during each ejection and over a full beat (cardiac stroke velocity) and over a full minute (cardiac output velocity). Formulae utilising the known relationship of aortic diameter to body height and weight, or direct measurements of aortic dimensions by echocardiography can then be used to calculate blood volume from blood velocity.

A method for calculating aortic flow velocity from the directly measured or indirectly measured arterial, aortic, or carotid pressure and/or diameter

waveform wherein the reflected component of the pressure wave is excluded and a classic formula (waterhammer) is used to calculate peak systolic flow velocity from the initial component of the central pressure waveform.

Preferably, ascending aortic pulse wave velocity as used in the waterhammer formula is measured directly, estimated from the delay from wavefoot to first systolic peak or shoulder, or taken from published data, from the US National Institute of Aging or another appropriate source for the subject's age.

Allowance is made for the reduced aortic velocity in late systole with aging, caused by reduced ventricular contractility in late systole, and attributable to increased left ventricular (LV) load and LV hypertrophy or disease, while allowing for any increase in ejection duration caused by hypertrophy.

Allowance is made for the further reduction in aortic velocity in late systole, caused by left ventricular weakening and relative change in the heart's pumping action from a "flow source" to a "pressure source".

Average velocity in the aorta is calculated for the period of ejection and the period of the cardiac cycle, and for other periods of time (eg. per second or per minute).

The method of the invention permits the aortic flow velocity, normalised for that individual, to be expressed in terms of volume by multiplying by aortic cross-sectional area determined from echocardiography, other methods, of from tables, then to be expressed as volumetric cardiac output per minute.

In order that the invention may be more readily understood and put into practical effect, reference will now be made to the accompanying drawings in which:-

Fig 1 shows the aortic pressure waveform,

Fig 2 shows the aortic flow waveform over one cardiac cycle,

Fig 3 is a nomogram showing the relationship between aortic pulse wave velocity and age,

Fig 4 is a nomogram showing the relationship between aortic root size and age,

Fig 5 is a nomogram for determining the body surface from height and mass,

Fig 6 shows the steps of the invention, and

Fig 7 shows the relationship between augmentation index and age in different arteries at different ages.

According to one embodiment of the invention, the pressure waveform in the ascending aorta is determined through recording the carotid pressure or diameter waveform, calibrating this according to the methods of Kelly and Fitchett (J Am Coll Cardiol 1992;20:952-63) or van Bortel et al (J Hypertens 2001;19:1037-44) or similar methods, and taking this as a surrogate of the aortic pressure waveform.

Alternatively, a generalised transfer function may be applied to the calibrated pressure wave recorded invasively or non-invasively in the brachial or radial artery, using the process described in US patent No. 5,265,011 or other appropriate methods.

Through use of differentials as described in the above publication or by other methods, the initial peak or shoulder of the aortic pressure waveform is identified and the height of this peak or shoulder (which typically is 90-120 msec after the pressure wavefoot) above the wavefoot itself is calculated. This is taken to represent the pressure wave generated by ventricular ejection before the return of significant wave reflection.

Alternatively, amplitude of this initial pressure peak or shoulder can be calculated directly from the radial or brachial pressure waves by exploiting the known relationship between brachial/ radial and aortic augmentation (Nichols and O'Rourke, McDonald's Blood Flow in Arteries, 4th ed., Arnold, London 1998; p.368 figure 16.20) (see figure 7) and subtracting aortic augmentation from aortic pulse pressure.

The "waterhammer formula" ($V = P/\rho.C$) is used to calculate the velocity (V) of blood at peak ejection from the pressure wave unaffected by wave reflection (P) assuming density of blood (ρ) = 1.05. The term C is aortic pulse wave velocity. This can be recorded directly as from delay in wavefeet between the carotid and femoral arteries, or indirectly from data prepared by Lakatta et al from the US National Institute of Aging (Lakatta EG. Cardiovascular Aging in Health. Heart Failure in the Elderly. In: Clinics in Geriatric Medicine 2000;16:419-43), which link aorta pulse wave velocity with age, and show no gender difference.

Other normal values e.g. Avolio et al., Circulation 1983;68:50-58; or Nichols and O'Rourke 1998, may be used instead. Examples of these data are shown in Fig 3. [For the Lakatta data, the following formula is used:- $C = 8.52 * age + 222$, where C is aortic pulse wave velocity in cm/sec].

The duration of ejection from wavefoot to cardiac incisura is measured and compared to the total cycle length. This allows for differences in the duration of left ventricular contraction and relaxation as seen under different conditions eg. change in heart rate. The incisura is determined from the recorded radial, brachial, subclavian or carotid waveform, using differentials or other methods. The ejection duration is typically in the region of 250-350 msec, and relative duration of systole 30-40% of the cardiac cycle.

Assuming no flow in diastole, one then has to consider the shape of the aortic flow wave, and how this is influenced by aging and weakening of the ventricular muscle. In the first aspect, it is assumed that peak flow is achieved at the already identified shoulder and that flow ceases at the identified incisura. It is also assumed that the area under this curve in a healthy normal person under age 60 equates to a rectangle characterised horizontally by the duration of ejection and vertically by 80% of peak forward flow velocity. It is further assumed no flow in diastole. This step is necessary on account of intermittency of cardiac contraction and relaxation.

The effects of aging are allowed for by assuming relatively lower forward flow velocity in the latter part of systole after the early flow peak, as shown by Nichols et al (Am J Cardiol 1985;55:1179-84). As a first approximation, the value of 80% is taken to reduce by an absolute value of 10% for each decade over age 60 – ie. to 60% at age 80 and 50% at age 90. More precise approximations can be made when more normal human aging data becomes available.

The effect of impaired left ventricular contraction on the pulse waveform (Westerhof and O'Rourke. J Hypertension 1995;13:943-52) is allowed for by reducing the value calculated above by absolute 10% if LV ejection fraction (LVEF) known to be below 25-40% (ie. from 80% at age 60 to 70%) and by absolute 20% if LV ejection fraction is known to be below 25% (ie. from 80% at age 60 to 60%). If cardiac failure is present and ejection fraction is not known, we use the first figure of 10% (as for LVEF 25-40%).

Calculated flow velocity is then determined per ejection (and per beat). This is normalised for body size since the waterhammer formula relates pressure change to velocity change. In each individual, velocity can be converted to volume flow (stroke volume in mls/beat) from measurement of

aortic cross-sectional diameter and area by ultrasound, or from the nomogram from Lakatta et al (Lakatta EG. Cardiovascular Aging in Health. Heart Failure in the Elderly. In: Clinics in Geriatric Medicine 2000;16:419-43) (see attached) which relates body height and weight to aortic cross-sectional area. From the Lakatta data, the formula [D = 0.0654 * age + 12.63] can be used, where D is diameter per square meter body surface area, and body surface area is available from nomograms (DuBois and DuBois, Arch Intern Med 1916;17:863) and Geigy Scientific Tables (attached). Cardiac output is calculated as stroke volume * heart rate (in litres/min).

The method described has other aspects, and it will be appreciated that variations and additions are possible within the spirit and scope of the invention. Previous applications of this type of method have used the waterhammer formula on central or peripheral pressure pulse waveforms. The specific novelty of this approach is that it takes account of the change in left ventricular ejection pattern which occurs with aging (as a consequence of early wave reflection and late systolic pressure augmentation), and the progressive change of the heart from a "flow source" to a "pressure source" with aging as afterload increases (Nichols et al. Am J Cardiol 1985;55:1179-84), and other further change which occurs as the ventricular muscle weakens through ventricular hypertrophy or from intrinsic cardiac (eg. coronary) disease (O'Rourke MF. Blood Pressure 1994;3:33-37). The approach also concentrates on scaled values of flow in terms of linear velocity rather than volume flow.

Other aspects of the invention allow direct measurement of aortic pulse wave velocity, or its estimation from the time to return of the reflected wave (London et al. Hypertension 1992;20:10-19), instead of from the NIA or other tables. Other aspects entail use of the calibrated carotid or upper limb pressure pulse waveform to determine the impulse generated by ejection

(without reflection) and of ultrasonic or other techniques to calculate aortic cross-sectional area. On account of different systematic effect of age on the proximal aorta that on the truncal arteries, it may be necessary to introduce a scaling term in the equations used to calculate peak velocity from pressure under different conditions. It may also be necessary to vary the constants presently proposed to describe the effect of aging and of heart failure on the arterial pulse.

Measurement of cardiac output or cardiac index (scaled to body dimensions as achieved here) is an important clinical measure, being increased in exercise and pregnancy, with thyroid overactivity, and with some forms of "hypertension", including "white coat hypertension". Cardiac index is reduced with blood or fluid loss, with pulmonary embolism and cardiac failure from multiple causes. Since the major function of the heart is to pump blood, measurement of the amount pumped is a valuable clinical sign. To determine this simply with logical physiological processes is an important advance.

Fig 1 shows a central (aortic or carotid) pressure waveform recorded directly or synthesised from a peripheral pressure waveform. The point 0 is the foot of the wave from which pressure rises smoothly up to a localised peak or shoulder at point 1, some 90-120 msec after the foot of the wave. Pressure may rise further after this point 1, but then declines to an inflection or incisura typically some 250-350 msec after the wavefoot. This incisura denotes closure of the aortic valve and the end of ventricular ejection. The pressure rise from point 0 to point 1 (P1 – P0) is determined by the flow ejection in the time T1-T0, by aortic pulse wave velocity and blood density according to the waterhammer formula. The flow velocity change from zero at the wavefoot to its peak and back to zero at the incisura is represented by the broken line. The peaks of pressure and flow correspond at point 1.

The flow velocity curve shown in Fig 2 in systole normally approximates to a rectangle (dotted lines) of base corresponding to ejection duration and height corresponding to 80% of peak flow. This alters with aging as left ventricular load increases and the ventricule hypertrophies. Ejection duration may increase, but the patterns of late systolic flow changes such that there is low velocity in later systole and average systolic flow typically falls to 60% of peak flow.

In cardiac failure the same phenomenon is seen with lower flow in late systole. The period of systole may also be decreased but this is directly measurable as reduction in ejection duration, and of ejection duration/ duration of cardiac cycle. Presently, the subtle change in the flow pattern can only be inferred from the lesser degree of augmentation than expected in late systole.

Fig 3 is a nomogram of the relationship between aortic pulse wave velocity and age from NIA studies (Lakatta EG. Cardiovascular Aging in Health. Heart Failure in the Elderly. In: Clinics in Geriatric Medicine 2000;16:419-43).

Fig 4 is a nomogram of the relationship between aortic diameter and body surface area from NIA studies (Lakatta EG. Cardiovascular Aging in Health. Heart Failure in the Elderly. In: Clinics in Geriatric Medicine 2000;16:419-43).

Fig 5 is a nomogram for the calculation of body surface area (Geigy Scientific Tables).

The steps of the method of the invention are shown in Fig 6 as follows:-

Step 1 Calculation of pressure rise in aorta caused by peak flow ejection (P) (multiple methods possible)

Step 2 Calculation of peak flow velocity (F) corresponding to (P) using water hammer formula

Step 3 Calculation of mean flow velocity in systole, by assuming that mean systolic flow = 80% of peak flow

Step 4 Allowance for effect of age on flow pattern, with reduced flow in late systole causing mean systolic flow to be < 80% of peak

Step 5 Allowance for effect of heart failure, with flow in late systole further reduced at any given age to << 80% of peak

Step 6 Calculation of mean cycle flow velocity as (mean systolic velocity) x Z

Where $Z = \frac{\text{period of systole}}{\text{period of cycle}}$

Step 7 Calculation of volume flow from mean cycle velocity and aortic cross sectional area (stroke volume)

Step 8 Calculation of cardiac output (L/min) by multiplication of stroke volume by heart rate

Fig 7 shows the relationship between augmentation index and age in different arteries at different ages. Augmentation index = augmented pressure / (initial pressure rise + augmented pressure).

Various modifications may be made in details of the method without departing from the scope and ambit of the invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method and device for calculating aortic flow velocity from the directly measured or indirectly measured arterial, aortic, or carotid pressure and/or diameter waveform. The reflected component of the pressure wave can be excluded so that a classic formula (waterhammer) can be used to calculate peak systolic flow velocity from the initial component of the central pressure waveform.

2. A method and device according to claim 1 wherein ascending aortic pulse wave velocity ad used in the waterhammer formula is measured directly, estimated from the delay from wavefoot to first systolic peak or shoulder, or taken from published data, from the US National Institute of Aging or another appropriate source for the subject's age.

3. A method and device according to claims 1 and 2 wherein allowance is made for the reduced aortic velocity in late systole with aging, caused by reduced ventricular contractility in late systole, and attributable to increased left ventricular (LV) load and LV hypertrophy or disease, while allowing for any increase in ejection duration caused by hypertrophy.

4. A method and device according to claims 1, 2 and 3, wherein allowance is made for the further reduction in aortic velocity in late systole, caused by left ventricular weakening and relative change in the heart's pumping action from a "flow source" to a "pressure source".

5. A method and device according to above claims wherein average velocity in the aorta can be calculated for the period of ejection and the period of the cardiac cycle, and for other periods of time (eg. per second or per minute).

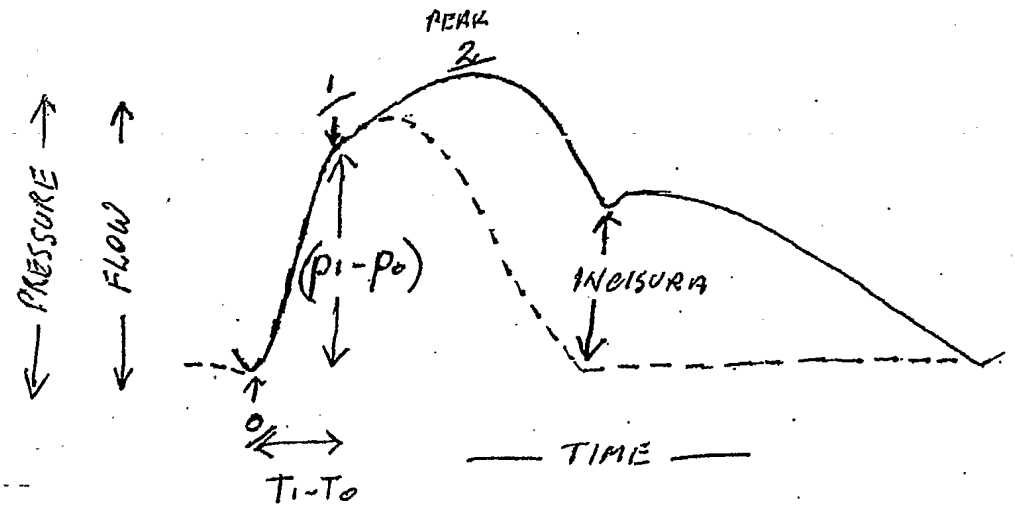
6. A method and device according to the above claims which permits the aortic flow velocity, normalised for that individual, to be expressed in terms of volume by multiplying by aortic cross-sectional area determined from echocardiography, other methods, of from tables, then to be expressed as volumetric cardiac output per minute.

7. A method for calculating aortic flow velocity substantially as hereinbefore described with reference to the accompanying drawings.

Dated this 5 day of March, 2004

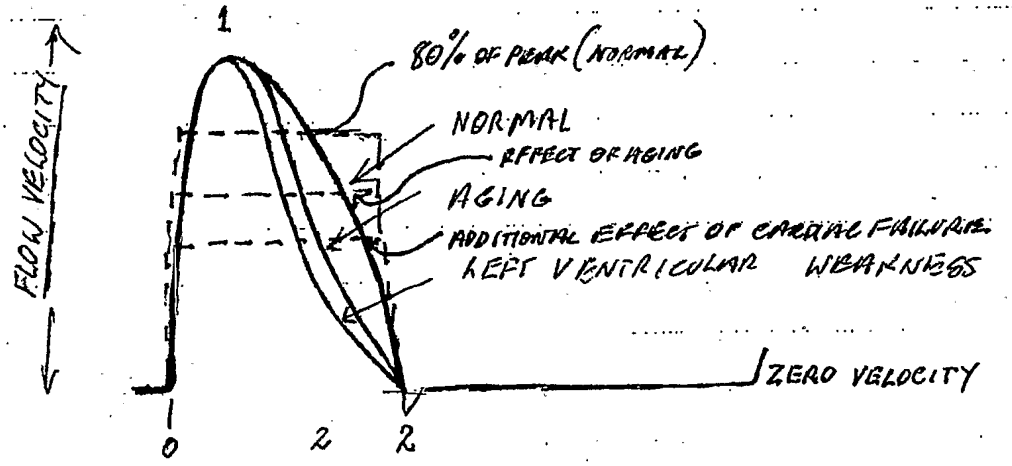
Michael Francis O'Rourke
Patent Attorneys for the Applicant
PETER MAXWELL & ASSOCIATES

FIG. 1



AORTIC PRESSURE WAVEFORM
(CAROTID PRESSURE AND DIAMETER WAVES ARE SIMILAR)

FIG. 2



AORTIC FLOW WAVEFORM OVER ONE CARDIAC CYCLE

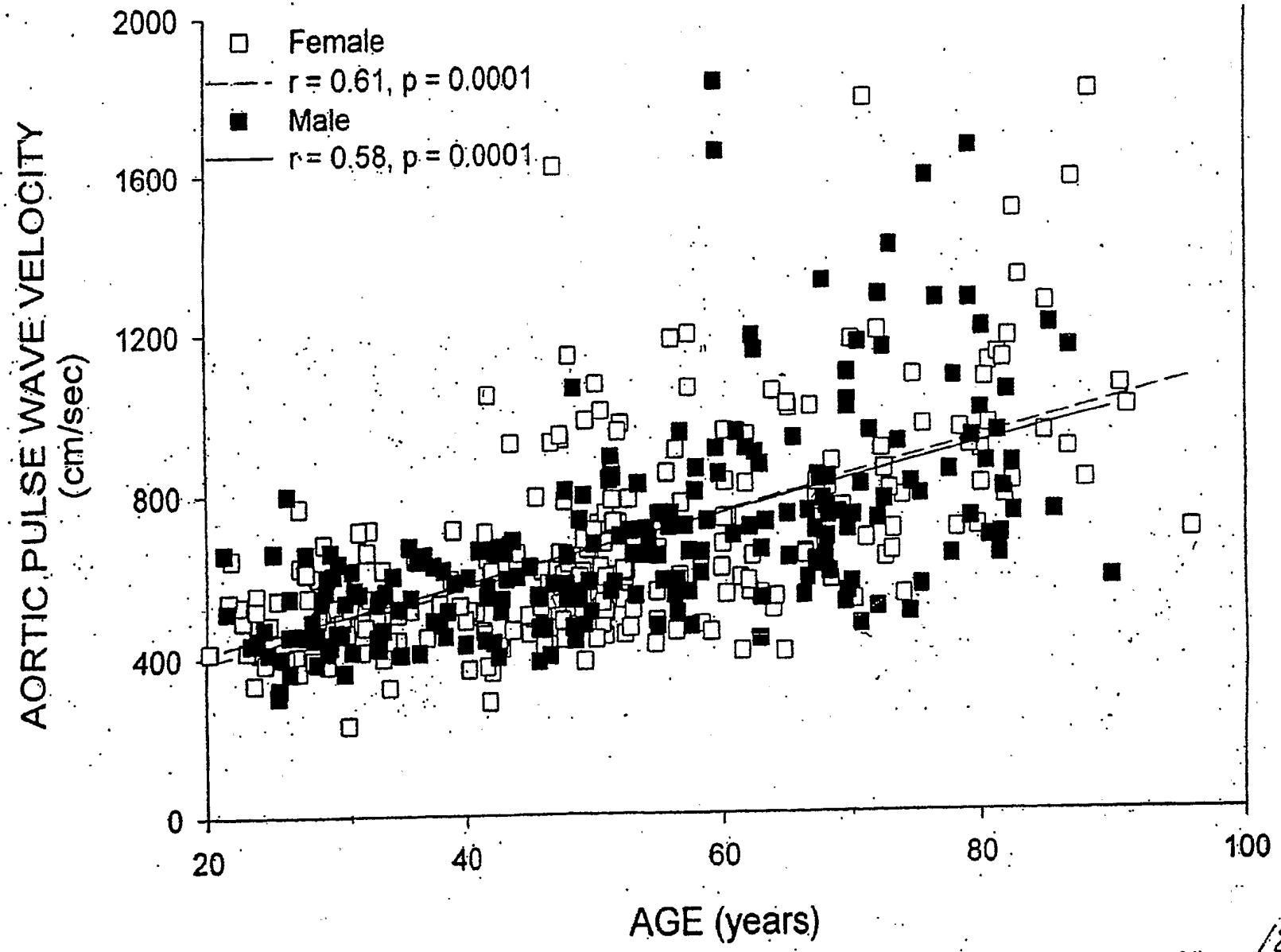

2000
1600
1200
800
400
0
20
40
60
80
100
Female
r = 0.61, p = 0.0001
Male
r = 0.58, p = 0.0001
AORTIC PULSE WAVE VELOCITY
(cm/sec)
AGE (years)

Fig. 3.

18.12B

18.9C

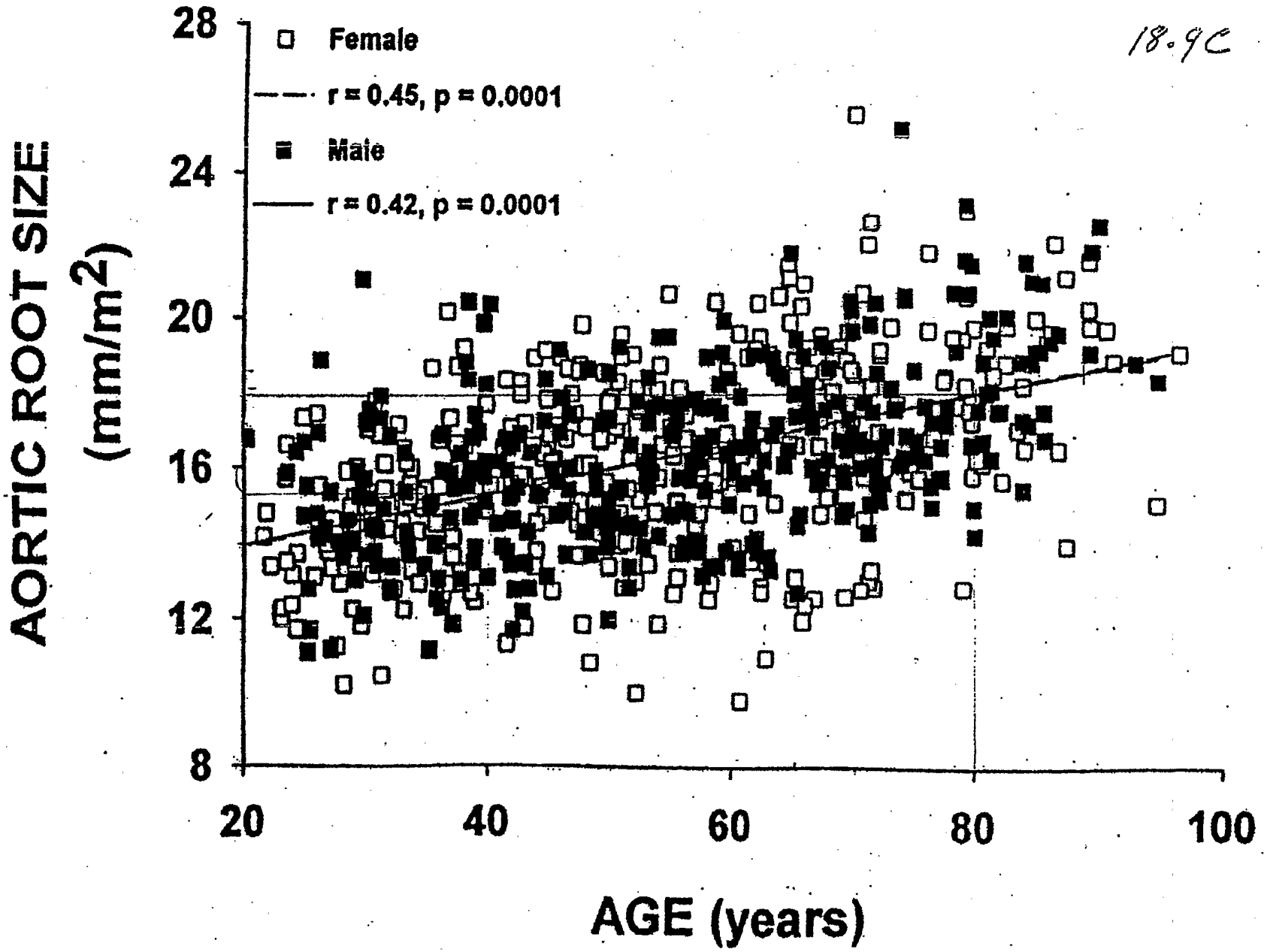
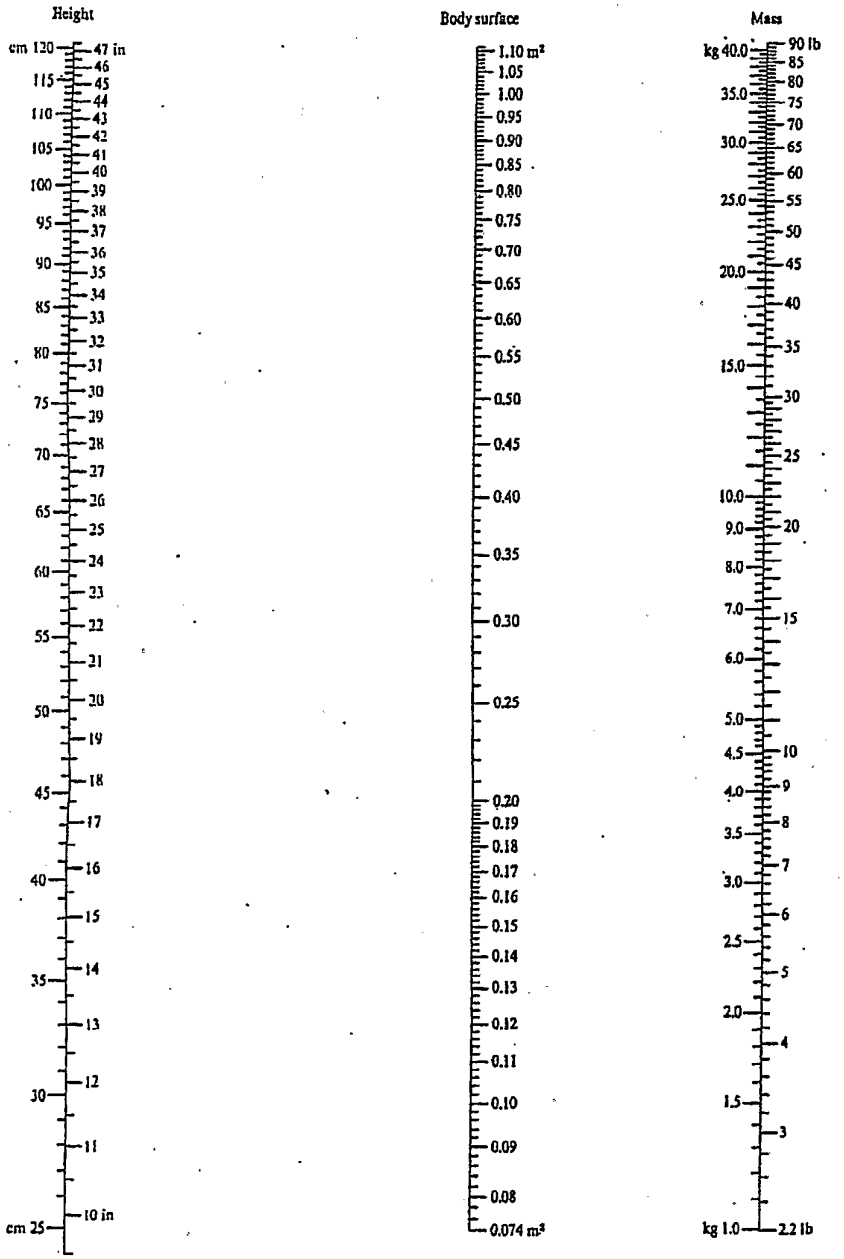

Female
r = 0.45, p = 0.0001
Male
r = 0.42, p = 0.0001
AORTIC ROOT SIZE (mm/m2)
28
24
20
16
12
8
20
40
60
80
100
AGE (years)

Fig. 4

Nomogram for determination of body surface from height and mass[1]



[1] From the formula of Du Bois and Du Bois, *Arch. Intern. Med.*, 17, 863 (1916): $S = M^{0.425} \times H^{0.725} \times 71.84$, or $\log S = \log M \times 0.425 + \log H \times 0.725 + 1.8564$ (*S*: body surface in cm², *M*: mass in kg, *H*: height in cm).

Nomogram for determination of body surface from height and mass[1]

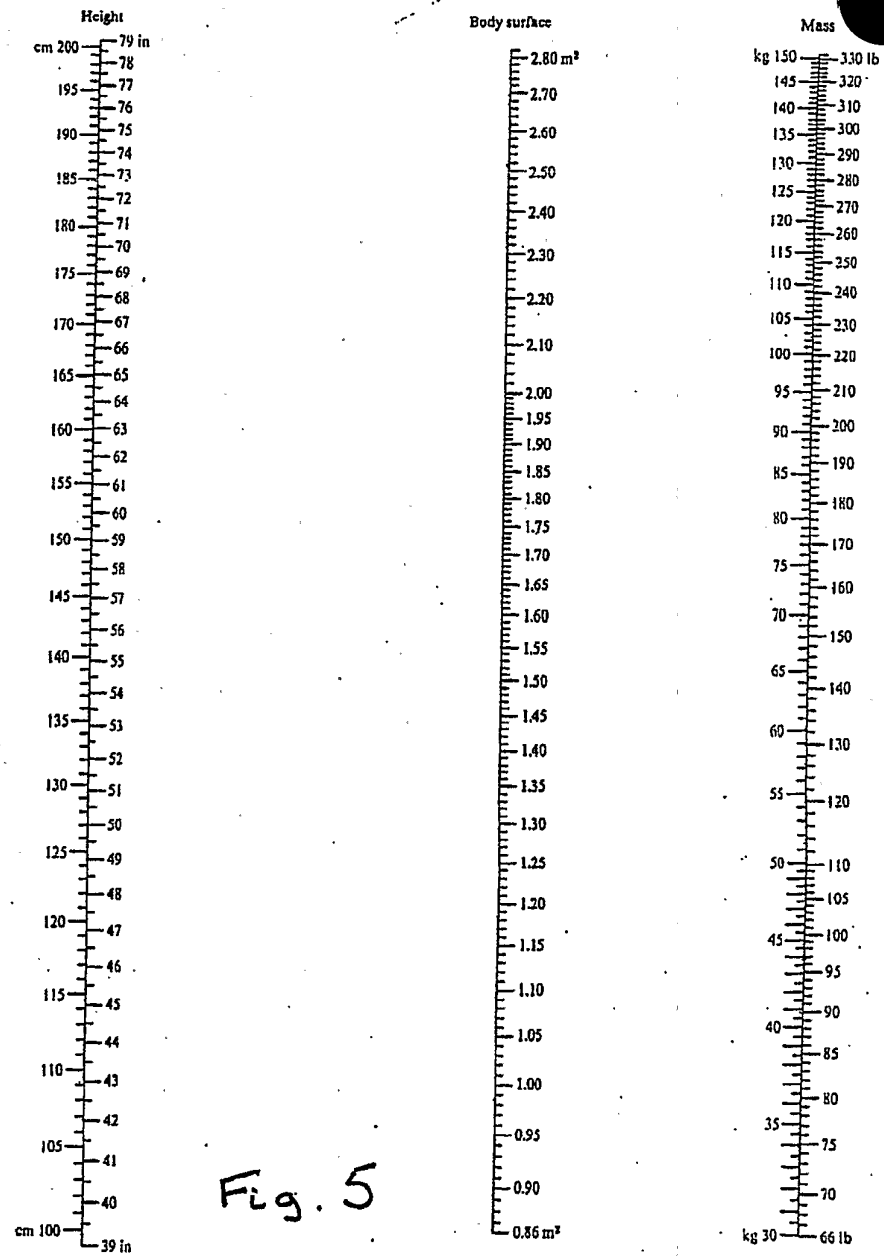
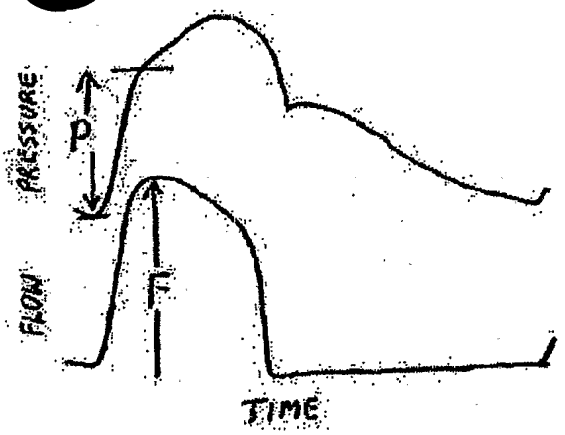
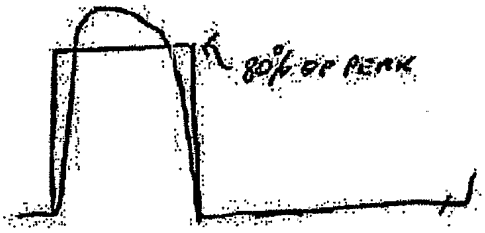
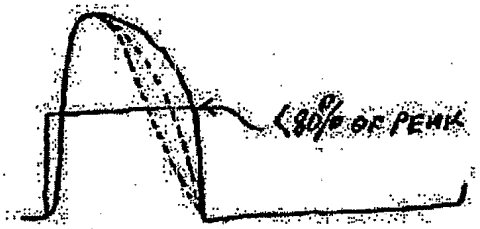


Fig. 5

[1] From the formula of Du Bois and Du Bois, *Arch. Intern. Med.*, 17, 863 (1916): $S = M^{0.425} \times H^{0.725} \times 71.84$, or $\log S = \log M \times 0.425 + \log H \times 0.725 + 1.8564$ (*S*: body surface in cm², *M*: mass in kg, *H*: height in cm).







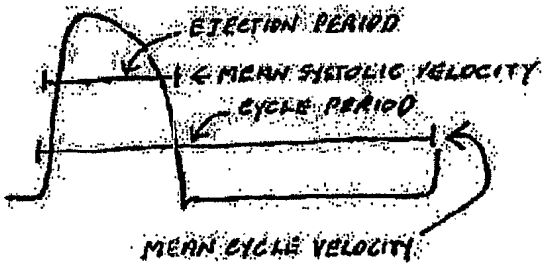


FIG 6

STEP 1 CALCULATION OF PRESSURE RISE IN AORTA CAUSED BY PEAK FLOW EJECTION (P) (MULTIPLE METHODS POSSIBLE)

STEP 2 CALCULATION OF PEAK FLOW VELOCITY (F) CORRESPONDING TO (P) USING WATER HAMMER FORMULA

STEP 3 CALCULATION OF MEAN FLOW VELOCITY IN SYSTOLE, BY ASSUMING THAT MEAN SYSTOLIC FLOW = 80% OF PEAK FLOW

STEP 4 ALLOWANCE FOR EFFECT OF AGE ON FLOW PATTERN, WITH REDUCED FLOW IN LATE SYSTOLE CAUSING MEAN SYSTOLIC FLOW TO BE (80% OF PEAK

STEP 5 ALLOWANCE FOR EFFECT OF HEART FAILURE, WITH FLOW IN LATE SYSTOLE FURTHER REDUCED AT ANY GIVEN AGE TO << 80% OF PEAK

STEP 6 CALCULATION OF MEAN CYCLE FLOW VELOCITY AS (MEAN SYSTOLIC VELOCITY) × Z WHERE $Z = \frac{\text{PERIOD OF SYSTOLE}}{\text{PERIOD OF CYCLE}}$

STEP 7. CALCULATION OF VOLUME FLOW FROM MEAN CYCLE ~~to~~ VELOCITY AND AORTIC CROSS SECTIONAL AREA (STROKE VOLUME)

STEP 8 CALCULATION OF CARDIAC OUTPUT (L/MIN) BY MULTIPLICATION OF STROKE VOLUME BY HEART RATE

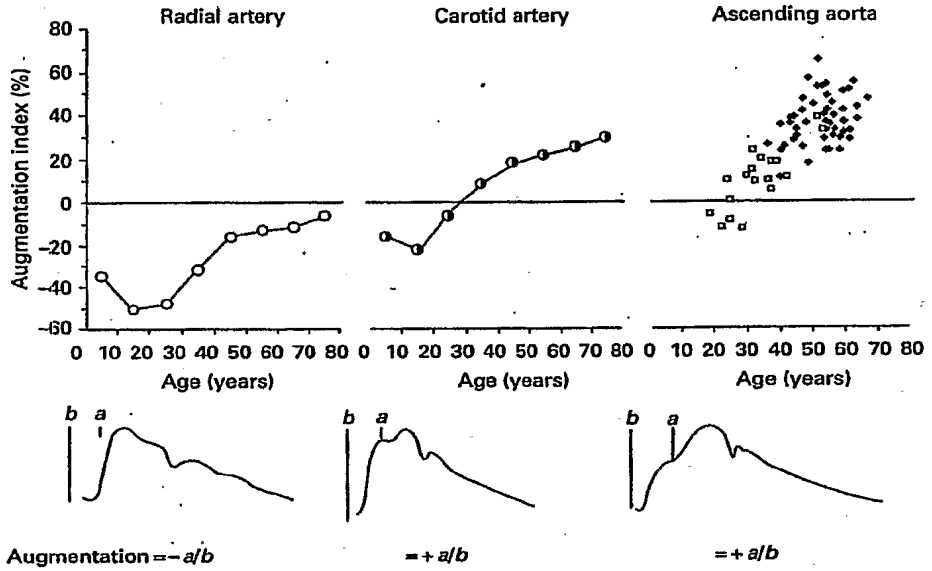


Fig. 16.20 Change of augmentation index (here shown as amplitude of shoulder to peak ÷ pulse pressure, as in the pressure waves displayed below) with age in the radial artery (left), determined by Kelly *et al.* (1989e); in the carotid artery (center), determined by Kelly *et al.* (1989b); and in the ascending aorta (right) from Murgo *et al.* (1980a;□) and Takazawa (1987;♦)

Fig. 7